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Recurrent Respiratory Papillomatosis Successfully Treated with Gefitinib: A Case Study

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Abstract *Background:* Recurrent respiratory papillomatosis (RRP) is a rare condition caused by infection of the respiratory tract mucosa with human papillomaviruses. The disease is characterized by a growth of mucosal papillomas, mostly in the laryngeal region and rarely in the more distal parts of the airways. The therapy is often difficult, including both mechanical removal of papillomas and pharmacological therapy. *Methods:* Presented in the article is a case of regression of papillomatosis in the larynx, trachea and lung parenchyma after administration of gefitinib, an endothelial growth factor receptor inhibitor. The literature review is added into this article to give more information about the etiology, clinical features and treatment. *Results:* The authors report a case of 42-year-old Caucasian female, recurrent respiratory papillomatosis was diagnosed in her first year of life. Papillomas were primarily diagnosed in the vocal cord region. Both pharmacological and frequently repeated invasive treatment brought no effective solution; by contrast, papillomas spread to the distal airways. A decision to administer gefitinib was made after other treatment modalities had failed. As early as two months later, the therapeutic effect was observed, with regression of both laryngotracheal and pulmonary involvement. *Conclusions:* Tyrosine kinase inhibitors of epidermal growth factor receptor represent a new treatment possibility for a long-term benefit for patients with recurrent respiratory papillomatosis in whom other modalities failed.

Keywords: *recurrent respiratory papillomatosis (RRP), HPV 6, HPV 11, gefitinib*

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1. Introduction

Drugs used in the treatment of recurrent respiratory papillomatosis (RRP) aim to inhibit the growth of papillomas or induce apoptosis in target cells. The currently used drugs are not clearly effective, which is particularly true for the long-term effect of the therapy. Recently, attention has therefore been given to novel molecules that could break the resistance of papilloma cells to pharmacological therapy. A new possibility that can be used in treatment is the fact that papilloma cells excessively express the endothelial growth factor receptor. It has turned out that inhibition of signaling pathways associated with activation of this receptor results in inhibited growth and apoptosis of papilloma cells [1].

Here we report a case of 42-year-old Caucasian female who had frequent critical airway obstructions caused by papillomas. When other treatment modalities failed we decided to start treatment with gefitinib.

A notable success is the fact that after the therapy was initiated, papillomas disappeared and laser disobliteration of the airways was not needed. As seen from the literature, this is the first case of successful treatment of a progressive form of recurrent respiratory papillomatosis with gefitinib in an adult patient.

2. Case Report

Reported is a case of a 42-year-old woman with no risk factors present who was diagnosed with laryngeal papillomatosis at the age of one year. Papillomas were localized in the vocal cord region. The symptoms were related to severity of the local finding, including permanent voice change – dysphonia to aphonia – and foreign body sensation in the throat. With papillomatosis progression, dyspnea or even stridor occurred, an irritating cough was intermittently present, associated with difficult to expectorate sputum when infectious complications developed. In the course of her disease, the patients

underwent more than 80 endoscopic procedures (initially, microsurgical papilloma excisions and, later, laser vaporization for papillomas). On two occasions, her clinical condition required tracheostomy (1x in childhood, then at the age of 35 years). Tracheal involvement was detected at 30 years of age in the form of small papillomas extending from the vocal cords to the upper third of the trachea. In 2002 (when aged 33 years), the patient was unsuccessfully treated with interferon alpha. She was referred to our department in 2004 when papillomatosis progressed in the trachea. Endoscopic vaporization with Nd:YAG laser was continued. In August 2007 a chest radiograph showed bilateral nodular shadowing (Figure 1). High-resolution computed tomography (HRCT) of the lungs showed multiple sites of lung parenchymal involvement manifested as cysts with thickened walls sized up to 18 mm. Some cysts were empty, others were partly or completely filled with a dense content. Histological samples collected during thoracoscopy confirmed pulmonary manifestation of RRP. Immunohistochemistry tests revealed strong membrane positivity for the epidermal growth factor receptor (EGFR) (Figure 2). Viral DNA analysis confirmed human papillomavirus (HPV) 11 infection. Later, additional tests for EGFR mutations (exon 19 deletion, L858R substitution) did not confirm their presence in these loci. Between June 2008 and August 2009, the patient was treated with immunomodulation therapy (IMMODIN, leukocyte lysate injections; then Isoprinosine tablets). The two drugs produced no effects and papillomas recurred. Moreover, a follow-up HRCT scan showed mild progression of the lung involvement. Further treatment included a recombinant vaccine against HPV 6, 11, 16 and 18 (3 x 0.5 mL injections of Silgard). At the same time, the patient received the antiviral cidofovir (Vistidine concentrate for solution for infusion) by both intratracheal (a 10-mL dose, of which 7 mL intralesionally and 3 mL topically on the mucosa; a concentration of 7.5 mg/mL) and inhalation (5 inhalations in a single session at a dose of 1 mg/kg of body weight) administration. A total of 4 cycles were administered at intervals of 4 weeks (November 2009 – March 2010). Bronchoscopy showed no regression, only a delayed growth of new papillomas that less frequently required treatment with laser. After completion of therapy, a follow-up HRCT of the lungs showed no changes in the size and number of lesions; one cavitary lesion was revealed. Five months after cidofovir therapy was completed, bronchoscopy revealed progression in papilloma frequency and sizes, requiring repeated laser treatment. A HRCT scan confirmed cavitary lesions in the lung parenchyma, with the cavities being filled with small amounts of fluid. The patient reported mild dyspnea and fatigue. In June 2011, gefitinib therapy was started, with a daily dose of 2x 250 mg [1]. As early as 2 months later, complete regression of vocal cord and tracheal papillomas was noted. After 1 year of therapy, gefitinib doses were reduced to 1 x 250 mg/day, with 1-month pauses introduced later. Repeated follow-up bronchoscopy confirmed the favorable finding of complete regression of papilloma in the vocal cord and trachea region (Figure 3). Chest radiograph was negative, cavitary lesion were empty of their pathological content and the cavity walls were thinner on HRCT scans (Figure 4). After 2 years, therapy was interrupted for 2 months. After gefitinib was discontinued, the patient's dysphonia worsened and bronchoscopy showed recurrent papillomas in the vocal cord region that were endoscopically removed. After gefitinib therapy was restarted, the problems resolved and papillomas in the vocal cords disappeared. Currently, gefitinib is administered at a dose of 250mg/day, the patient is followed up regularly, without any signs of disease recurrence.

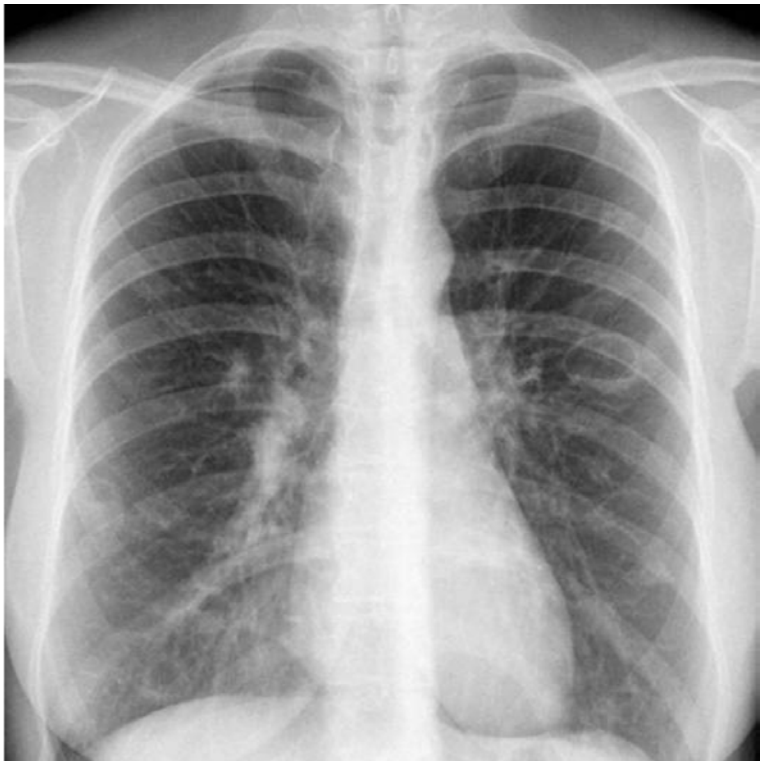

Figure 1. chest radiograph (August 2007), bilateral nodular shadowing, biggest lesions manifested as a cysts

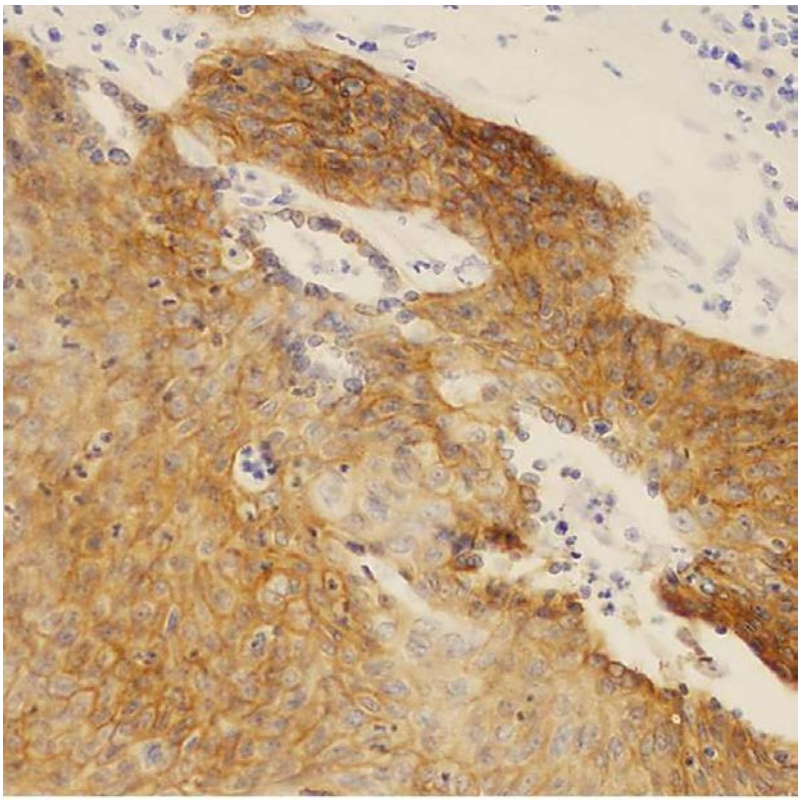

Figure 2. continual membrane positivity EGFR 2+, microscope magnification 200x

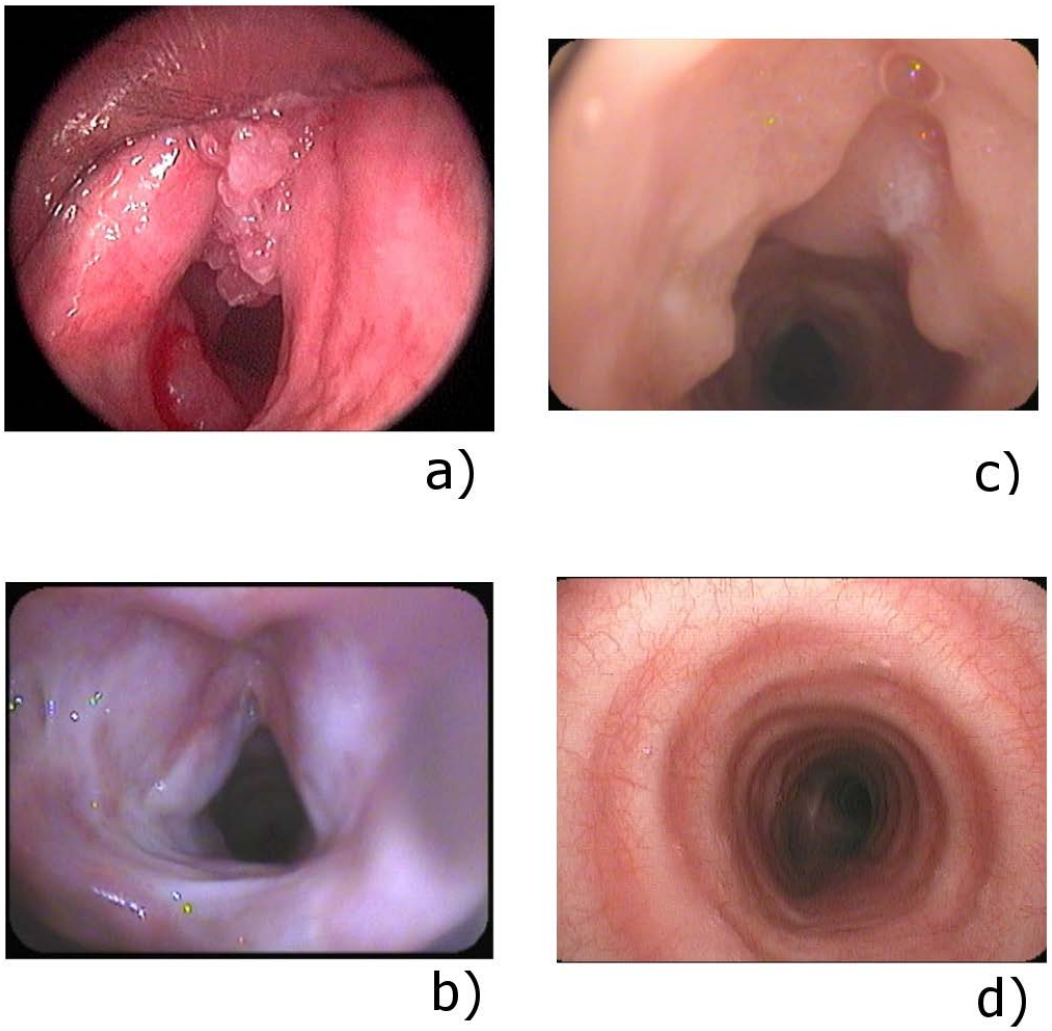

Figure 3. comparison of endoscopical findings: a) and c) vocal cords and trachea before treatment, b) and d) identical organs after gefitinib therapy

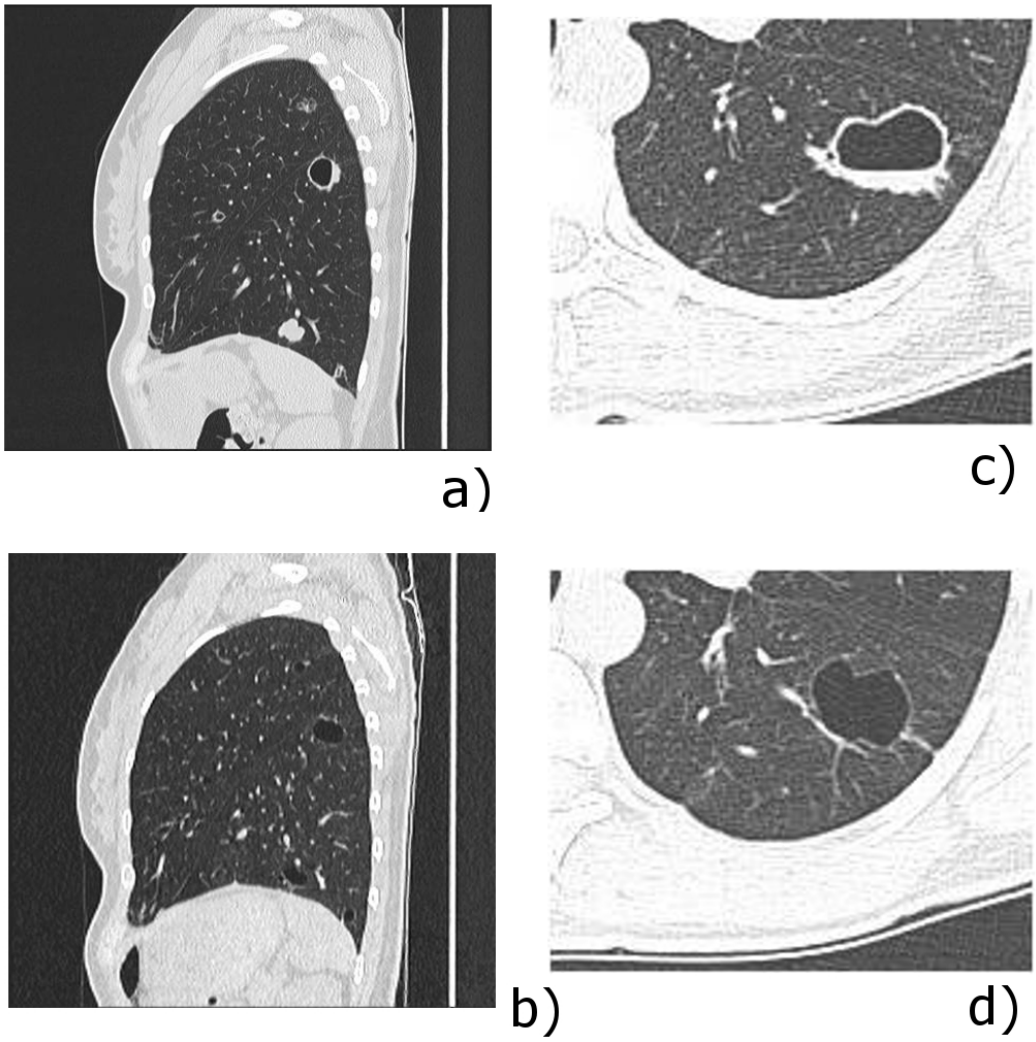

Figure 4. comparison of CT findings: a) and c) CT scans before treatment, August 2010; b) and d) CT scans after treatment, August 2011

3. Discussion

RRP is a chronic disease of the respiratory tract caused by HPV. The condition is characterized by a growth of multiple mucosal papillomas, mostly in the laryngeal region but other parts of the airways or the adjacent portions of the digestive tract may be affected as well [2,3,4]. Although the disease is primarily benign its clinical course is rather unpredictable, with a tendency towards relapses and progression. Spontaneous regression of the condition is also possible. Apart from physical harm and challenging therapeutic procedures, patients are frequently under significant mental strain and the costs of treatment are very high [2]. Malignant transformation of RRP to squamous cell carcinoma has been observed as well. Various authors reported the risk for lung cancer to range from <1% to 14%. A higher risk for malignant transformation is probably associated with smoking and previous radiotherapy, with spontaneous transformations being rare [5,6]. Most frequently, the development of RRP is contributed to by HPV 6 and HPV 11; sporadically, both viruses are present. There have been reports of other HPV types (13, 16, 18, 31, 33, 35, 39, 40, 45 and 56) being detected in papilloma tissue with molecular genetic methods [2,7,8,28].

The age distribution curve is biphasic. Most frequently, the condition develops before 5 years of age (75%), being the most common benign tumor of the larynx in childhood. In adults, the incidence peaks in the 4th decade of life. The age range of symptom onset and diagnosis is from the early postnatal period to 84 years of age. If the condition is diagnosed before 12 years of age it is referred to as juvenile-onset RRP (JORRP). The other cases are adult-onset RRP [9]. According to data published in the USA, the incidence rates in children and adults are 4.3/100,000 and 1.8/100,000, respectively. Conversely, an older Danish study reported a slightly lower incidence in children than in adults (3.62/100,000 vs. 3.94/100,000) in 1965–1984. A much lower incidence of 0.24/100,000 (a prevalence of 1.11/100,000) in children aged 14 years and younger in 1994–2007 was found by a large Canadian study [10,11,12]. While there is no gender predominance in JORRP, the adult-onset form is slightly more common in males [9].

Although papillomas may occur anywhere along the respiratory system, the larynx is by far the most frequently affected organ (>95% of cases). Tracheal involvement as reported by various authors ranges from 2% to 26% of cases, with papillomas typically spreading downwards from the laryngeal region. Involvement of the bronchi and lung parenchyma ranges from <1% to 5% and is associated with a poorer prognosis of the disease.

Papillomas may also spread to the mouth and paranasal sinuses and have been observed in the upper digestive tract as well [3,5,13,14,15,17]. At a microscopic level, the areas most susceptible to HPV infection are the so-called squamocolumnar junctions where the squamous epithelium meets the columnar epithelium. By this mechanism, papillomatosis may occur at tracheostomy sites where iatrogenic squamocolumnar junction may be created [16].

Given the most frequent papilloma location, the first clinical symptom is a change in voice, with hoarseness or even aphonia in the most severe cases. Stridor, indicative of airway obstruction, is usually the second symptom, being inspiratory first and biphasic later. Other manifestations include chronic cough, foreign body sensation in the throat, hemoptysis, infectious complications, failure to thrive, dyspnea – either chronic or paroxysmal, difficulty in swallowing and, in severe cases, respiratory failure. In very young children, voice changes may only be small, with only a weakened cry. The mean time period from onset of symptoms to diagnosis is approximately 1 year. The condition may be misdiagnosed as bronchial asthma, laryngitis, bronchitis or singer's nodules [2,3,17]. Deaths from asphyxia associated with massive laryngeal papillomatosis has been reported but, fortunately, such cases are rare [18].

The principal diagnostic method is endoscopy with papilloma biopsy and histological examination with DNA typing (polymerase chain reaction, in situ hybridization) [17]. Lung involvement may be detected by chest radiography, also suitable for regular follow-up of the lesions. Accurate information about lung parenchyma involvement, particularly the presence of early lesions, is provided by a CT scan of the chest. This method is also suitable for assessing changes in the lung parenchyma following systemic therapy. Pulmonary spread of RRP is most frequently characterized by multiple solid or cystic nodules. These may enlarge, their contents may be emptied and they may change into cystic, cavitary lesions. To elucidate the anatomy of the laryngeal, tracheal and bronchial regions, virtual bronchoscopy is used [14,19].

A more severe course of the disease is associated with HPV 11. Moreover, besides the larynx, the trachea and lung parenchyma are more frequently affected by HPV 11 infection [17]. Other studies pointed to the fact that a factor that is more significantly associated with a more severe clinical course of the disease is the age of the child at its onset. Since the mean age of children infected with HPV 11 is lower at the time of diagnosis (2.4 years in HPV 11 and 3.4 years in HPV 6), the prognosis of these infections is also more serious [20].

Unlike other human papillomavirus infections in which the route of transmission of infection is under study and has not been clearly confirmed, the most frequent cause for the onset of RRP is considered to be vertical transmission from mother to child during birth. This is when infected secretions in the birth canal are in contact with the respiratory tract mucosal epithelium [2,4].

Children of mothers with a history of genital warts are at a highly increased risk for JORRP. Other risk factors include primigravidity, maternal age under 20 years (possible association with a longer time of the newborn's exposure to the virus in case of prolonged delivery) and a lower socioeconomic status. It is known that in only a small proportion of HPV-infected children, RRP is clinically manifested. Therefore, other factors for developing the infection are assumed, such as an individual's immune system properties, duration and level of viral exposure or local trauma (intubation, extraesophageal reflux) [2,3,4,21]. Giving birth by cesarean section does not protect against developing the disease completely as intrauterine transmission of the infection is likely to occur. Whereas some studies showed a lower risk for the development of RRP in infants born by cesarean section to mothers with HPV infection in the anogenital region, this was not confirmed by other studies [21,22]. The etiology of transmission of the virus in adulthood has not been clearly demonstrated. Sexual transmission is assumed as well as potential activation of HPV infection acquired at birth [9].

At the present time, no therapeutic method is known to be conclusively effective. Treatment is multimodal, combining various therapeutic procedures. Interventional endoscopic techniques comprise especially laser therapy and, less frequently, cryotherapy and microdebridement. If necessary, tracheostomy is indicated for vocal cord involvement [2]. Pharmacological therapy includes a broad spectrum of agents with various actions, administered either alone or, in most cases, as adjuvant therapy after an invasive procedure. Although no clearly effective and safe drugs are currently available, most authors advocate adjuvant therapy [23,31]. The criteria for initiating adjuvant therapy are as follows: more than four invasive procedures per year, local or distant spread of the disease and rapid regrowth of papillomas after their removal [24]. The most frequently used drug is the antiviral cidofovir. It is mainly applied locally, that is intralesionally; systemic administration is used in multisystem involvement [24]. Kiverniti et. al. analyzed treatment response in 11 studies (complete or partial remission, with fewer endoscopic interventions) carried out in both adult and pediatric patients treated with cidofovir which was achieved in nearly 85% of cases [23]. So far, however, these data have not been supported by large randomized studies or meta-analyses. Conversely, a double-blind placebo-controlled study by McMurray et. al. did not show a statistically significant benefit of adjuvant cidofovir therapy [29]. There is anecdotal evidence of the use of other antivirals, such as ribavirin. Acyclovir is used to treat other viral infections (herpes simplex virus 1, Epstein-Barr virus, cytomegalovirus) aggravating the course of RRP; otherwise, due to the biological basis of its effect, it has no impact on HPV [24]. Yet other agents used in the treatment of RRP are mainly interferon alpha and indole-3-carbinol. Moreover, retinoids, photodynamic therapy, mumps vaccine and other drugs have also been tried. With an exception of interferon studies that failed to prove a long-term effect, mostly smaller non-randomized groups of patients were studied and despite excellent results of some studies, the evidence of effectiveness was equivocal [4]. Also investigated were the effects of multivalent HPV (6,11,16,18) vaccines on the onset, course and incidence of RRP. [2] Based on the knowledge of increased expression of EGFRs as well as cyclooxygenase-2 (COX-2) and its product, prostaglandin E2, new options in the treatment of RRP include EGFR inhibitors (erlotinib, gefitinib, cetuximab) and COX-2 inhibitors (celecoxib). [25,26] Highly vascularized

papilloma tissues largely express the vascular endothelial growth factor (VEGF), thus resembling tumor tissues. This is where VEGF inhibitors may be applied (a pilot study of intralesional bevacizumab) [27]. A trial has been performed to evaluate the effectiveness of gene therapy (a recombinant fusion protein of heat shock protein 65 from *Mycobacterium bovis* BCG and E7 protein from HPV 16) [30]. If extraesophageal reflux increasing the recurrence rates is present, therapy with histamine 2 blockers or proton-pump inhibitors is recommended [3]. Ionizing radiation or other DNA-damaging agents are contraindicated in the treatment of RRP as they increase the risk for development of malignant transformation [32].

Gefitinib is a low-molecular-weight selective inhibitor of EGFR tyrosine kinase. In clinical practice, it is used to treat patients with locally advanced or metastatic non-small-cell lung cancer with EGFR-activating mutations [2].

In the presented case, gefitinib was administered based on the finding that in papilloma cells, endothelial growth factor receptors are overexpressed. Subsequent inhibition of signaling pathways inhibits the cell cycle, promotes apoptosis and inhibits angiogenesis. Children with RRP successfully treated with EGFR inhibitors have been documented in several case reports [1,25,26]. As of now, data on the treatment of adults with the condition are unavailable.

Reasons for treating RRP with EGFR: [1,33,34,35]
• Papilloma cells express high rates of EGFR.
• Constitutive activation of EGFR results in impaired cell differentiation. The level of proliferation is not higher than in uninfected cells but impaired terminal differentiation lead to accumulation of cells with an uncontrolled cell cycle and minimal expression of specific keratins and filaggrins. Because of the changes, infected cells are relatively resistant to apoptosis.
• Papilloma cells exhibit pathological changes in several other signaling pathways associated with EGFR.
• EGFR kinase inhibitors induce growth inhibition, lead to differentiation and apoptosis of immortalized keratinocytes.

4. Conclusion

This is the first description of successful gefitinib therapy administered to an adult woman who suffered from a progressive form of RRP caused by HPV 11 for 40 years. The biological characteristics of papillomas suggest that gefitinib, or EGFR inhibitors, represent a new hope for a long-term benefit of treatment for patients in whom other modalities failed. In most cases, the therapy is well tolerated and the adverse effects are acceptable.

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Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors have been involved in drafting the manuscript and revising it critically, giving final approval of the version to be published.

References

[1] Bostrom B, Sidman J, Marker S, Lander T, Drehner D. Gefitinib therapy for life-threatening laryngeal papillomatosis. Arch Otolaryngol Head Neck Surg 2005; 131: 64-67.

[2] Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008; 118: 1236-1247.

[3] Harman EM, Mosenifar Z, Sharma S, Talavera F, Manning HL, Rice TD. Recurrent respiratory papillomatosis. http//:emedicine.medscape.com/article/302648. Date last update: Nov 20, 2013. Date last accessed: Aug 14, 2014.

[4] Tasca RA, Clarke RW. Recurrent respiratory papillomatosis. Arch Dis Child 2006; 91: 689-691.

[5] Hammoud D, El Haddad B. Squamous cell carcinoma of the lungs arising in recurrent respiratory papillomatosis. Respiratory Medicine CME 2010; 3: 270-272.

[6] Cook JR, Hill DA, Humphrey PA, Pfeifer JD, El-Mofty SK. Squamous cell carcinoma arising in recurrent respiratory papillomatosis with pulmonary involvement: emerging common pattern of clinical features and human papillomavirus serotype association. Mod Pathol 2000; 13: 914-918.

[7] Penaloza-Plascencia M, Montoya-Fuentes H, Flores-Martinez SE, Fierro-Velasco FJ, Penaloza-Gonzales JM, Sanchez-Corona J. Molecular identification of 7 human papillomavirus types in recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2000; 126: 1119-1123.

[8] Stamataki S, Nikolopoulos TP, Korres S, Felekis D, Tzangaroulakis A, Ferekidis E. Juvenile recurrent respiratory papillomatosis: still a mystery disease with difficult management. Head Neck 2007; 29: 155-62.

[9] Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. APMIS 2010; 118: 450-454.

[10] Armstrong LR, Derkay CS, Reeves WC. Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP Task Force. Arch Otolaryngol Head Neck Surg 1999; 125: 743-748.

[11] Lindeberg H, Elbrond O. Laryngeal papillomas: the epidemiology in a Danish subpopulation 1965-1984. Clin Otolaryngol Allied Sci 1990; 15: 125-131.

[12] Campisi P, Hawkes M, Simpson K; Canadian Juvenile Onset Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 2010; 120: 1233-1245.

[13] Zawadska-Glos L, Jakubowska A, Chmielik M, Bielicka A, Brzewski M. Lower airway papillomatosis in children. Int J Pediatr Otorhinolaryngol 2003; 67: 1117-1121.

[14] Frauenfelder T, Marincek B, Wildermuth S. Pulmonary spread of recurrent respiratory papillomatosis with malignant transformation: CT findings and airflow simulation. Eu J Radiol Ex 2005; 56: 11-16.

[15] Batra PS, Hebert RL 2nd, Haines GK 3rd, Holinger LD. Recurrent respiratory papillomatosis with esophageal involvement. Int J Pediatr Otorhinolaryngol 2001; 58: 233-238.

[16] Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 1993; 102: 580-583.

[17] Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004; 114(Suppl.)104: 1-23.

[18] Balazic J, Masera A, Poljak M. Sudden death caused by laryngeal papillomatosis. Acta Otolaryngol Suppl 1997; 527: 111-113.

[19] Aggunlu L, Erbas G. Recurrent respiratory papillomatosis with lung involvement. Diagn Interv Radiol 2009; 15: 93-95.

[20] Buchinsky FJ, Donfack J, Derkay CS, Choi SS, Conley SF, Myer CM III, McClay JE, Campisi P, Wiatrak BJ, Sobol SE, Schweinfurth JM, Tsuji DH, Hu FZ, Rockette HE, Ehrlich GD, Post JC. (2008) Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. PLoS ONE, 3 (5), e2263.

[21] Silverberg MJ, Thoresen P, Lindeberg H, Grant LA, Shah KV. Condylomata in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003; 101: 645-652.

[22] Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infect Dis J 1998; 17: 372-376.

[23] Kiverniti E, Sevdalis N, Rachmanidou-Doran A. A systematic review on recurrent respiratory papillomatosis: clinical effect and duration of benefit of different treatment modalities. Oncol Rev 2010; 4: 35-42

[24] Shebab N, Sweet BV, Hogikyan ND. Cidofovir for the treatment of recurrent respiratory papillomatosis: a review of the literature. Pharmacotherapy 2005; 25: 977-989.

[25] Limsukon A, Susanto I, Hoo GW, Dubinett SM, Batra RK. Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy. Chest 2009; 136: 924-926.

[26] Loyo M, Pai SI, Netto GJ, Tunkel DE. Aggressive recurrent respiratory papillomatosis in a neonate. Int J Pediatr Otorhinolaryngol 2008; 72: 917-920.

[27] Zeitels SM, Lopez-Guerra G, Burns JA, Lutch M, Friedman AM, Hillman RE. Microlaryngoscopic and office-based injection of bevacizumab (Avastin) to enhance 532 nm pulsed KTP laser treatment of glottal papillomatosis. Ann Otol Rhinol Laryngol Suppl. 2009 Sep; 201: 1-13.

[28] Mammas IN, Sourvinos G, Vakonaki E, Giamarelou P, Michael C, Spanidos DA. Novel human papilloma virus (HPV) genotypes in children with recurrent respiratory papillomatosis. Eur J Pediatr 2010; 169: 1017-1021.

[29] McMurray JS, Connor N, Ford CN. Cidofovir efficacy in recurrent respiratory papillomatosis: a randomized, double-blind, placebo-controlled study. Ann Otol Rhinol Laryngol 2008; 117: 477-483.

[30] Derkay CS, Smith RJ, McClay J, van Burik JA, Wiatrak BJ, Arnold J, Berger B, Neefe JR. HspE7 treatment of pediatric recurrent respiratory papillomatosis: final results of an open-label trial. Ann Otol Rhinol Laryngol 2005; 114: 730-737.

[31] Ruan SY, Chen KY, Yang PC. Recurrent respiratory papillomatosis with pulmonary involvement: A case report and review of the literature. Respirology 2009; 14, 137-140.

[32] Dyrstad SW, Rao KA. Recurrent Respiratory Papillomatosis (RRP)-Juvenile Onset. Clin Med Oncol 2008; 2: 481-486.

[33] Vambutas A, Di Lorenzo TP, Steinberg BM. Laryngeal papilloma cells have high levels of epidermal growth factor receptor and respond to epidermal growth factor by a decrease in epithelial differentiation. Cancer Res 1993; 53: 910-914.

[34] Johnston D, Hall H, Di Lorenzo TP, Steinberg BM. Elevation of the epidermal growth factor receptor and dependent signaling in human papillomavirus-infected laryngeal papillomas. Cancer Res 1999; 59: 968-974.

[35] Steinberg BM, Meade R, Kalinowski SS, Abramson AL. Abnormal differentiation of human papillomavirus-induced laryngeal papillomas. Arch Otolaryngol Head Neck Surg 1990; 116: 1167-1171.